REMARKS

A. Status of the Claims

Claims 17-33 were examined in the Action. New claims 34-37 have been added. Thus, claims 17-36 are currently pending. Support for the new claims can be found in the specification at, for example, page 5, last paragraph; page 6, first complete paragraph; and in the claims as originally filed. No new matter has been added.

B. Amendment to the Specification

The first paragraph on page 7 of the specification has been amended to correct a typographical error. Support for this amendment may be found in FIG. 1 of the specification.

C. The Claims are Enabled

Claims 17-33 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Action indicates that the specification is enabling for claims directed to a transgenic rat whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID NO: 9, said DNA operably linked to a promoter, wherein the promoter is a mouse Thy-1 promoter, wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology occurs in the rat when compared to normal rats (Action, p. 4, first paragraph). The Action asserts, however, that there is insufficient description to enable the full scope of the current claims. Applicants traverse this rejection.

The Action appears to focus on the following three areas in the enablement rejection: (1) the scope of the promoter enabled by the specification; (2) the scope of the cDNA molecule coding for N- and C- terminally truncated tau molecules enabled by the specification; and (3) the

scope of the transgenic non-human animal enabled by the specification. Applicants address each of these areas below.

1. Promoters

The Action asserts that the specification is enabling only for a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID NO: 9, said DNA operably linked to a promoter, wherein the promoter is a mouse Thy-1 promoter. In other words, the Action is asserting that it would require undue experimentation for a person of ordinary skill in the art to make and use a DNA construct with any promoter other than a mouse Thy-1 promoter. Applicants traverse.

The Action's position in this regard is inconsistent with the legal standard for enablement. Enablement must be evaluated from the position of a person of ordinary skill in the art. The specification teaches that a "construct" is a recombinant nucleic acid sequence, generally recombinant DNA sequences, operably linked to tissue specific or general promoter, that is generated for the purpose of the expression of a specific nucleotide sequence(s) in mammalian cells, or is to be used in the construction of other recombinant nucleotide sequences (Specification, p. 6). Thus, in light of the specification, a person of ordinary skill in the art would understand that a "DNA construct" as recited in claim 17 contains a promoter operably linked to the cDNA molecule coding for N- and C- terminally truncated tau molecules. A person of ordinary skill in the art would further understand that the promoter in the DNA construct is a promoter suitable for expression in mammalian cells.

The specification further teaches methods for the preparation and evaluation of DNA constructs that may be used in the presently claimed invention (Specification, p. 12, ln. 12-38). With regard to promoters for eukaryotic expression, this passage teaches the use of appropriate

promoters for brain expression or ubiquitous expression. Additional disclosure of cloning truncated tau coding by incorporating appropriate restriction sequences so that it can be cloned under general or tissue specific promoters in an eukaryotic expression vector is disclosed in the specification at page 21, lines 8-36. As noted in the specification, these methods are described in Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor Laboratory Press, 1989) (Specification, p. 21, ln. 34-36).

Numerous promoters are known and readily available to those in the art. Examples of some promoters that have been used to drive transgene expression in the central nervous system of various mammals are provided in the review article by Fitzsimons *et al* (Methods 28:227–236 (2002); *see e.g.,* Tables 1 and 2). The cytomegalovirus (CMV) promoter, for example, had been used to drive the expression of several different transgenes in the central nervous system of rat, mice, and monkeys (Fitzsimons, Table 1). In addition, the publication by Lewis *et al.* (Nat Genet. 25(4):402-5 (2000)) shows the expression of human tau protein in mice using the mouse prior promoter (MoPrP).

It would require only routine cloning procedures, such as those described in the present specification or in Sambrook *et al.*, to place a cDNA molecule coding for N- and C-terminally truncated tau molecules under the control of an appropriate promoter. Such routine cloning does not constitute undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Accordingly, the scope of promoters encompassed by the current claims is enabled by the specification.

2. The cDNA Molecule Coding for N- and C-Terminally Truncated Tau Molecules

The Action asserts that the specification is only enabling for a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID NO: 9. Applicants traverse.

It appears that the Examiner's rationale in wanting to limit the claims to only the sequence of SEQ ID NO: 9 is that the Examiner believes that this is the sequence used in transgenic rat line #318. Applicants would like to clarify that the sequence in transgenic rat line #318 ***comprises*** SEQ ID NO: 9. SEQ ID NO: 9 encodes the minimally truncated tau protein, which corresponds to nucleotides 741-930 (Specification, FIG. 1). The construct in transgenic rat line #318 contains nucleotides 277-999 of tau. This was previously explained in Applicants' Response dated 1/10/07 (p. 9). Applicants note, however, that the nucleotide range recited in the previous response was arrived arithmetically as nucleotides 279-999, which in incorrect since amino acid 93 actually starts at nucleotide 277. As mentioned above, the construct in transgenic rat line #318 contains nucleotides 277-999 of tau. Applicants have attached an enlarged view of the amino acid and nucleotide numbering at the beginning and end of the truncated region (nt 1-276) and the tau sequence in transgenic rat line #318 (nt 277-999) to demonstrate this. Accordingly, the sequence in the construct in transgenic rat line #318 comprises not only SEQ ID NO: 9 but also SEQ ID NOs: 3, 6, 7, and 8.

In addition, the inventors have developed a further transgenic rat line, line #24, which contains a cDNA coding for human tau protein that is shorter by 93 nucleotides (31 amino acids) than the cDNA coding for human tau protein in transgenic rat line #318. As described in the attached declaration from Dr. Filipcik ("Filipcik Declaration"), the transgene construct used in the generation of transgenic rat line #24 was prepared by ligation of a cDNA coding for human tau protein truncated at amino acid positions 93-302 (based on isoform 44) into the mouse Thy-1 gene downstream of the brain promoter/enhancer sequence (Filipcik Declaration, para. 4). Amino acids 93-302 correspond to nucleotides 277-906 (Filipcik Declaration, para. 4). The sequence used for transgenic rat line #24 corresponds to SEQ ID NO: 12 in the specification.

SEQ ID NO: 12 was isolated from tau isotype 44, whereas SEQ ID NO: 9 was isolated from tau isotype 43 (*see* Specification, FIG. 1). Accordingly, the numbering of the nucleotide sequences in SEQ ID NOs: 9 and 12 is somewhat different. SEQ ID NO: 12 comprises SEQ ID NO:9 as shown in the specification where the sequence of SEQ ID NO: 9 can be found in the sequence for SEQ ID NO: 12 at page 10 of the specification beginning at the 15th nucleotide in the 7th line of SEQ ID NO: 12 and ending at the 22nd nucleotide on the 1st line of page 11. Thus, the truncated tau cDNA molecule used to generate rat line #24 is encompassed by the current claims as it is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; and the truncated tau cDNA molecule comprises SEQ ID NO: 9 (nucleotides 741-930).

The DNA construct used in generating transgenic rat line #24 encodes a protein, which has neurofibrillary pathology producing activity when expressed in brain cells of animals, as evidenced by the fact that transgenic rat line #24 exhibits neurofibrillary pathology. In particular, transgenic rat line #24 developed neurofibrillary lesions in the brain stem, spinal cord, primary motor cortex, and hippocampus (Filipcik Declaration, para. 5). Neurological examinations showed similar features in both the #24 and #318 transgenic rat lines. For example, the onset and progression of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 is almost identical (Filipcik Declaration, para. 8). Transgenic rats from line #24 were also shown to suffer from early cognitive impairment in an object recognition test (Filipcik Declaration, para. 8).

Transgenic rat line #24 is, therefore, further evidence of a transgenic non-human animal having germ and/or somatic cells which comprise a DNA construct comprising a cDNA

molecule coding for N- and C-terminally truncated tau molecules, wherein: the cDNA molecule is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; (2) the cDNA molecule comprises SEQ ID No. 9; and (3) the DNA construct encodes a protein, which has neurofibrillary (NF) pathology producing activity when expressed in brain cells.

The scope of the cDNA molecule coding for N- and C-terminally truncated tau molecules encompassed by the claims is enabled at least by the direction provide in the specification (*see* Applicants' previous response at pages 11-13) and the existence of working examples.

3. The Transgenic Non-Human Animal

The Action asserts that the specification is not enabled for any transgenic animal other than rat. In addition, the Action asserts that there is no correlation for association between expression of any derivative of the Alzheimer's tau proteins in rat with any relevant characteristics or useful phenotype other than neurofibrillary pathology. Applicants traverse.

Neurofibrillary pathology, which is present in transgenic rat lines #318 and #24, is the most important and earliest immunohistochemical finding in Alzheimer's disease (*see* Braak *et al.*, Acta Neuropathol (Berl), 112(4):389-404 (2006)). Fig. 10 and the accompanying descriptions on pages 20-21 and 25 of the present specification depict a comparison of neurofibrillary pathology in the brains of patients suffering from Alzheimer's disease and those observed in the brain of transgenic rat line #318. Equivalent pathological structures were observed when comparing the two samples (*Id.; see also* Figs. 6-8 and their accompanying descriptions at pp 19-20). Accordingly, a transgenic animal that exhibits neurofibrillary pathology is a useful model for Alzheimer's disease.

Moreover, neurofibrillary pathology is not the only Alzheimer's disease related characteristic of the transgenic rats disclosed in the present specification. As described in the declaration of Dr. Filipcik provided with Applicants' response filed on January 10, 2007, the expression of truncated tau in rats is a net inducer of oxidative stress, which is another pronounced symptom in human Alzheimer's disease (*see* para. 11 of Dr. Filipcik's declaration filed on January 10, 2007). This is further confirmed in a paper by Cente *et al.* (Eur J Neurosci., 24(4):1085-90 (2006)), which discloses that truncated tau induces oxidative stress. Additionally, transgenic rat line #318 exhibits hypertension – up to 220 mm/Hg (Filipcik Declaration, para. 11). It is also easy to induce diabetes in transgenic rat line #318 by using a specific diet formulation (Filipcik Declaration, para. 11). Thus, the transgenic animals encompassed by the current claims are useful models of Alzheimer's disease because they exhibit the most important and earliest immunohistochemical finding in Alzheimer's disease (*i.e.*, neurofibrillary pathology) and they exhibit other pathological features associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes (Filipcik Declaration, para. 11).

In addition to rats, a variety of animal models would be suitable Alzheimer's disease (AD) models since AD associated neurofibrillary (NF) pathology, based on paired helical filaments (PHF), occurs in a number of animals. For example, Hartig *et al.* (European Journal of Neuroscience, Vol. 25, pp. 69–80, 2007) shows that PHF-like tau occurs in hamsters, which parallels the situation in AD (abstract). Hartig also notes that PHF-like tau was observed in ground squirrels (p. 69, right col., para. 2).

Huang *et al.*, (Brain Research 771, 1997, 213–220) describes neurofibrillary tangles based on abnormal tau in rabbits. The proteins have a molecular structure that closely resembles

that of primates, thus making such an animal system of relevance for human neurodegenerative disease like AD (abstract, p. 214, left col., para. 2, p. 219, left col., para. 2).

Gotz (Brain Research Reviews 35 (2001) 266–286) describes the use of murine models expressing tau as system for the dysfunction of tau and neurodegeneration and dementia based on neurofibrillary lesions (abstract, p. 275, right col., item 4.3). In addition, Lewis *et al.*, (Nat Genet. 2000 Aug; 25(4):402-5)) describes the formation of AD related NF tangles through expression of mutant human tau in mice (abstract). These reference demonstrate that a variety of animals are capable of exhibiting NF pathology and, therefore, are suitable for the study of NF pathology and Alzheimer's disease.

In view of the above, the claims are enabled for non-human transgenic animals and the evidence demonstrates that such animals exhibit characteristics that make them suitable models for Alzheimer's disease.

4. The Hrnkova Reference

The Action alleges that the Hrnkova reference teaches a lack of nexus between transgenic rats with human truncated tau protein and any Alzheimer's disease. There is, however, no basis for such an allegation. The Hrnkova reference only serves to further demonstrate the usefulness of a transgenic animal encompassed by the current claims as a model for NF pathology and Alzheimer's disease.

Hrnkova specifically states that "rat transgenic expression of human truncated tau, derived from sporadic Alzheimer's disease, led to the development of AD tau cascade. The cascade was represented by extensive neurofibrillary pathology satisfying several histopathological and biochemical criteria used for identification of neurofibrillary degeneration in AD...." (paragraph bridging pages 206-207). Hrnkova further states that the studies

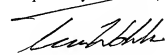
described in the publication "show[] that human truncated tau, when expressed in rat neurons, had dramatic effect on rat neurobehavioral phenotype." (p. 207, col. 1). More specifically, Hrnkova demonstrates that the expression of the truncated tau protein induced neurofibrillary changes leading to the progressive deterioration of neurobehavioral functions including spatial memory retention decline, sensorimotor coordination impairment and alterations in reflex responses (p. 209, col. 2, 1st para.; *see also* p. 210, col. 2, 1st full para.).

5. Summary

To be enabling within the meaning of 35 U.S.C. § 112, the application must contain a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. For the reasons set forth above, the present specification satisfies this requirement. Applicants, therefore, request the withdrawal of this rejection.

The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Truncated part:

Nucleotides: 1-276
AA: 1- 92

Fragment:

Nt: 277 - 999
AA 93 - 333